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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/668,788	09/22/2000	Frank P. Wolter	MAIWAM2.001CP1	2349

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EXAMINER	
RAO, MANJUNATH N	
ART UNIT	**PAPER NUMBER**
1652	16

DATE MAILED: 01/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/668,788	WOLTER ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 13-23* is/are pending in the application.

4a) Of the above claim(s) *13-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 18-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-6, 13 to 23 are still at issue and are present for examination. Claims 1-6, and 18-23 are now under consideration. Claims 13-17 remain withdrawn from consideration as being drawn to non-elected invention.

Applicants' amendments and arguments filed on 11-15-02, paper No.15, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Sequence Compliance

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. It is particularly noted that applicants fail to provide SEQ ID NOS to sequences disclosed n the specification. For example see page 6, 8, 24, 25. See particularly 37 CFR 1.821(d).

Specification

The amendment filed on 11-15-02 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: a) "60% identical to the sequence selected from the group consisting of SEQ ID NO:2 and 4" in claim 22 and b) more than 80% identical .....SEQ ID NO:2 and 4" in claim 23. A perusal of the specification provides support for 50%,

70%, 90% and 99% sequence identity. However Examiner was unable to find support for the amendment claiming 60% or 80% sequence identity to SEQ ID NO:2 and 4.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1 and 22 and claims 2, 4-6 and 18-21 and 23 which depend from claims 1 and 22 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 1 and 22 are directed to a process of production of glycolipids by transferring a nucleic acid molecule that codes for a protein having the activity of a processive diacylglycerol glycosyltransferase to cell or organisms. The word "organisms" encompasses humans also and thereby reads on a non-statutory subject matter. Therefore the above claims are rejected. Amending the claim to read as "non-human organisms" would overcome this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 22-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the process of producing glycolipids such as the diacylglycerols (mono, di, tri and tetraglucosyl or the respective glycosyl compounds),

glycosylceramides (mono and di-glycosyl or the respective glucosyl compounds), steryl glucosides (mono and di- glucosyl or their respective glycosyl) and glucosylphosphotidylglycerol (mono and di-) does not reasonably provide enablement for a process of producing any or all types of glycolipids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-3 and 22-23 are so broad as to encompass the process of making any glycolipid. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of glycolipids broadly encompassed by the claims. The specification is limited to teaching use of the above enzyme for producing few glycolipids but provides no guidance with regard to production of all other types of glycolipids using the provided enzyme (for example the complex glycolipids of bacterial cell wall) nor provides a teaching of other enzymes for the synthesis of other glycolipids. Since glycolipids comprise a diverse group of molecules with different glycosyl groups and different lipid acceptor groups and since applicants have not shown that all these types of glycolipids can be produced by the single enzyme provided, one of ordinary skill in the art requires a knowledge

of and guidance with regard to methods and reaction conditions required and additional enzymes if any, for producing the diverse group of glycolipid compounds and detailed knowledge of the ways in which the given enzyme can be used for such a process. However, in this case the disclosure is limited to process of producing only few of the glycolipids.

The specification does not support the broad scope of the claims which encompass the process of producing all glycolipids because the specification does not establish: (A) a rational and predictable scheme for process of producing all or any glycolipid using the enzyme provided; and (B) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a process of making any glycolipid. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the use of the enzyme for producing all glycolipids is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicants have traversed the above rejection asserting that claims are enabled and that the specification teaches those skilled in the art to make and use the full scope of the claimed invention without undue experimentation. Applicants also argue that Examiner has not understood their invention. Respectfully, Examiner disagrees with both arguments of the applicants. First of all applicants while simply arguing that Examiner has

not understood their invention, do not provide any supporting argument as to in which way Examiner has misunderstood their invention. Examiner reiterates that the specification does not enable one skilled in the art to make all or any glycolipids using the transformed organism provided by the applicants. Applicants further argue that amended claim 1 now defines the process for production of glycolipids as one using a processive lipid glycosyltransferases and therefore is enabled. While amendment to claim does define the enzyme, such an amendment does not render the claim fully enabled to make any or all types of glycolipids. The term "glycolipids" is a very broad term. Furthermore, applicants continue their redundant and tangential argument that by defining the nucleic acid molecule that is transferred and expressed in the transgenic cells/organism and also defining the claimed process "in terms of the processive enzymatic activity of the used lipid glycosyl transferase that is able to successively transfer hexose residues to a lipid acceptor the claims are enabled by the specification". Examiner respectfully disagrees. By defining the claimed process by redefining the enzyme property used in the process or the nucleic acid encoding such an enzyme, applicants have not enabled the claims. This is because such a definition still fails to provide enablement for synthesizing any or all types of glycolipids. Therefore, Examiner continues to maintain the above rejection.

Claims 1-6, 18-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process of making specific glycolipids using enzymes with SEQ ID NO:2 or 4, with a processive diacylglycerol glycosyltransferase (PDG) activity, does not reasonably provide enablement for such a process using any PDG from any or all sources or using any PDG enzyme isolated from any strain of *B.subtilis* or *S.aureus* or any PDG

enzyme having an amino acid sequence that is either 60% or 80% identical to SEQ ID NO:2 or 4.. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-6, 18-23 are so broad as to encompass a process which uses any PDG from any strain of *B.subtilis* or *S.aureus* or any PDG from any source including recombinants, variants and mutants. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of PDGs broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence to obtain the desired activity, requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary

structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim. The disclosure is limited to a process in which the amino acid sequences of only two PDGs are used.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple sources or to screen for multiple substitutions or multiple modifications, or as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any PDGs or any PDGs of any strain of *B.subtilis* or *S.aureus* because the specification does not establish: (A) a rational and predictable scheme for isolating and using any PDG from any source; (B) regions of any or all PDG protein structure which may be modified without effecting its activity; (C) the general tolerance of PDGs to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any amino acid residue in any PDG with an expectation of obtaining the desired biological function; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including all or any PDG from any and all sources. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of PDGs having the desired enzymatic characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicants have traversed the above rejection arguing that it should be understood that the processive activity of the enzymes according to the invention is a novel feature that was never described in the prior art and that this application for the first time described and characterized such an enzyme and provides the proof by describing the enzymes isolated from *S.aureus* and *B.subtilis*. Applicants argue that these two examples provide enablement for the full genus of such enzymes. Examiner respectfully disagrees with such an argument. Glycosyltransferases with processive activity in the lipid biosynthesis activity were known in the art. Examiner refers applicants to the review article of Saxena et al., (J. Bacteriology, 1995, Vol. 177(6):1419-1424, specifically page 1419, column 1, Ist para) which recognizes two types of glycosyltransferases, one of which is a processive glycosyltransferase for which the acceptor molecule could be a carbohydrate or a lipid. Therefore, while enzymes with SEQ ID NO:2 or 4 may be novel, claims directed to all (isolated from any source) or any such enzymes (including mutants, variants and recombinants) do not become enabled just by providing two examples. As such claims are directed to any and all such enzymes isolated from

any or all sources and applicants have not provided guidance to isolate and characterize such an enzyme from any or all sources which includes all microorganisms, plants, animals and viruses. Examiner disagrees with applicants view that just because their invention is a "pioneering invention" their claims are fully enabled. Examiner also disagrees with applicants' argument that using the disclosed teachings and the methodology those skilled in the art can easily make and use any PDG from any source. This is because not all sources are similar to either *B.subtilis* or *S.aureus*. Several sources need specific alterations from the method disclosed and applicants have not provided any information as to how their method can be altered to suit the isolation and characterization of the enzyme from any or all sources. For all the reasons above, the above rejection is maintained.

Claims 1-6, 18-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-6, 18-23 are directed to a process of producing glycolipids using any processive diacylglycerol glycosyltransferase or by using any processive diacylglycerol glycosyltransferase with an amino acid sequence that is either 60% or 80% identical to SEQ ID NO:2 or 4. Claims are rejected under this section of 35 USC 112 because the claims are directed to a process of producing any glycolipid using a genus of polypeptides derived from SEQ ID NO:2 or 4 including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue in SEQ ID NO:2 or 4 and fragments

of SEQ ID NO:2 or 4 that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of SEQ ID NO:2 or 4 for the above purpose has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the structure of all the polypeptide sequences encompassed by the claims, including fragments and variants within the scope of the claimed genus. The genus of polypeptides used in the claims is a large variable genus including peptides and polypeptides which can have a wide variety of structure. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses a method of making glycolipids using only two species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office action, applicants have traversed the above rejection arguing that the specification describes the claimed invention. Applicants quote page numbers where the specification "provides guidance sufficient to describe the full scope of the claimed invention including teaching numerous variations in the polypeptide sequences" (page 7 of the response). Such an argument is confusing to the Examiner, because it is not clear whether

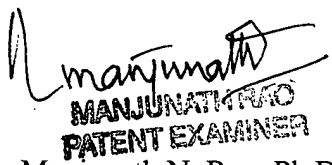
applicants are arguing against the written description rejection or against scope of enablement rejection. Applicants further provide examples of short stretch of amino acid sequences. Applicants argue that these examples are identical with the amino acids of the proteins from *B.subtilis* and *S.aureus*. However, there is o information as to the source of such amino acid sequences. It appears that applicants are arguing out of context. As discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case the claimed genera of Claims 1-6, 18-23 includes species which are widely variant in structure and function because of the extremely large number of sources (all microorganisms, i.e., bacteria fungi, algae, protozoa, yeasts etc., all plants and all animals and all

viruses). The genus of polypeptides claimed to be used in claims 1-6 and 18-23 is structurally and functionally diverse as it encompasses polynucleotides encoding polypeptides with glycosyltransferase activity,(including variants, mutants and recombinants). As such, neither the description of the structure and function of SEQ ID NOS: 2 and 4 (including the few amino acid sequences on page 6 of the specification) nor the disclosure solely structural features present in all members of the genus is sufficient to be representative of the attributes and features of the entire genus. Therefore the above rejection is maintained.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



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1/16/03